UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,055	12/31/2003	Yoko Motoda	1686-0108P	8334

2292 7590 03/10/2005

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

3/07/05 AA

Office Action Summary	Application No.	Applicant(s)	
	10/748,055	MOTODA ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 November 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/23/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgment is made of an amendment/response, filed 11/23/2004, canceling claims 1-13 and adding new claims 14-33. All objections/rejections not repeated herein are hereby withdrawn. As new grounds of rejection are set forth, this action is non-final.

Information Disclosure Statement

Previously, several references were presented in an Information Disclosure Statement (IDS), but no copies of said references were of record or no translation was provided for foreign language references. In the response filed, 11/23/2004, Applicants have resubmitted an IDS with translations provided for some of the foreign.

The Kigawa reference has been crossed through as not considered because it is a foreign language document and the only translation provided is for the abstract. Since the entire reference is cited in the IDS then for the reference to be considered a translation of the entire document is required for it to be considered. In addition, the Japanese document (JP 04-91790) has not been considered as it is solely presented in a foreign language with no translation provided.

Drawings

The drawings were received on 11/23/2004, replacing Fig. 4. However, the replacement drawing appears to be an exact duplicate of the figure as originally presented, thus is also obscure and unintelligible.

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the features/characteristics of the replacement drawing are not discernible.

The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 14 to 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

The following grounds were not made previously. Base claims 14, 15, 17, 32 and 33 are directed to primers, which anneal to 5' and 3' "terminal regions", but it is unclear what sets the boundaries for said terminal regions. For example, it is unclear to what extent two 5' sense primers share a particular region. The specification teaches that the 5' primer may have "a sequence common to a part of the 5' terminal side [of the other sense primer... ". (e.g., p. 6, last ¶ bridging to p. 7). The only other reference to "terminal regions" is limited to overlapping "second DNA fragment" and "first DNA fragment" thus is not germane to the sense primers that are the source of the vagueness. (e.g., Spec., p. 8). As such, the specification does not further clarify what are the boundaries for said terminal regions. As such, as written the claims are vague and indefinite, thus making indeterminable the claims' metes and bounds.

Claim 14 recites the phrase, "the first DNA fragment" which confers ambiguity in regard to defining the claims' metes and bounds. As written, it is unclear to which fragment the limitation "first" is referring.

For example, the preamble recites an "amplified DNA fragment" and primers are recognized as DNA fragments as well, thus any one of such fragments could be interpreted as a "first DNA fragment". It would be remedial to replace the limitation "first" with "template" so as to distinctly and particularly define the claim's metes and bounds.

Claim 17 recites "the first DNA fragment" in subpart *ab*, but it is unclear to which first DNA fragment this limitation is referring. The body of the claim that precedes subpart *ab* recites the phrase, "a template comprising a first double-stranded or single-stranded DNA" and the phrase, "a first amplified DNA fragment". Because of this ambiguity the claims' metes and bounds are indeterminable.

As written claim 22 is vague and indefinite, where the claim is directed to a method of amplifying DNA using recombinant microorganisms or culture broth comprising the first template DNA. The claim could be interpreted to mean that the PCR reaction mixture actually contains recombinant microbes (e.g., bacteria, yeast) in a method of template DNA amplification. It is unclear how the necessary components of the reaction mixture (e.g., $MgCl_2$, polymerase) would gain access to the DNA inside the microorganisms. The specification does not in any manner teach that the PCR mixture contains microorganisms or culture broth elements. In fact, the only reference to utilization of such elements is in the context of the expression (not PCR) assay, where *E. coli* extract used in a cell-free system to facilitate template expression (i.e., transcription and translation). Therefore, as written the claim's metes and bounds are indeterminable.

Claim 23 recites "primer component" which does not find antecedent support in base claim 17. Claim 17 refers to sense and antisense primers, not primer components.

The term "component" implies that an additional element that is encompassed within the primer molecule is intended.

Claim 32 recites the term, "the template" in subpart *ii*, which confers ambiguity. The only template DNA recited in the claim is in subpart *a*, which according to subpart *aa*, encodes a protein or a fragment of a protein. As such, such a template cannot be transcribed as is required in subpart *ii*. Does Applicant mean that the amplified DNA molecule (subpart *c*) comprising the overlapped DNA fragments containing regulatory elements, to be the template for *in vitro* transcription? The claim should be properly amended to clarify which template is to be transcribed in subpart *ii*, because as written, the claim is vague and indefinite.

Claim 33 recites phrases, "the first DNA fragment" (subpart *ab* and *ac*) and "the DNA fragment" (subpart *c*), which confers ambiguity in determining the claim's metes and bounds. Either phrase can be interpreted to be referring to the two distinct DNA fragments in subpart *I* (i.e., template DNA or amplified DNA). Therefore, as written the claim is vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent;
> or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 14-19, 21, 23-25 and 32-33 rejected under 35 U.S.C. 102(b) as being anticipated by Lanar et al. (WO 92/07949; see whole document).

Generally the claims are directed to a cell-free or *in vitro* process of protein production utilizing PCR generated template. The action steps or components for the claimed methods are interpreted as broadly as reasonable considering all claims are delimited using open language (i.e., *comprising*). In other words, the steps or components are not temporally or spatially delimiting. The claims are more particularly directed to methods of amplifying DNA fragments comprising a template DNA, a first sense primer and a second sense primer containing 3' terminal sequence that is the same as the 5' region of said first primer and a third antisense primer (claim 14). Additional claims are directed to the method comprising a template mixture of a first, second and third fragment (concentrations from 5 to 2,500 pmol/L), as well as the aforementioned primers, where the second and third fragment have overlapping regions 5' and 3' respectively to the first DNA fragment (claim 15).

Furthermore, with respect to the limitations of 3' or 5' terminal sequence, the region defined as terminal sequence is interpreted as broadly as reasonable in light of the non-exclusive teaching provided in the specification (p. 6, last ¶ bridging to p. 7; indicating the 5' primer may have "a sequence common to a part of the 5' terminal side [of the other sense primer..." Therefore, even a single sequence that overlaps as between a first and second sense primer, meets the required claimed limitation of a "second sense primer which has a 3' terminal sequence that is the same as at least a 5' portion of the first sense primer". (e.g., claim 14).

Lanar et al. teach a method utilizing expression PCR to produce templates for *in vitro* protein production.

More particularly, the reference teaches that at least two sense primers are used, as well as two antisense primers. (e.g., Figs. 5-6; pp. 10-11, Example 1; p. 12, Example 2). Furthermore, the sense primers would have at least a single nucleotide sequence in common. The reference teaches that primers A (sense primer) and B (antisense primer) are used to amplify the gene to be expressed. (e.g., p. 5, l. 11). In addition, Primer A has nucleotides at it s 5' end complimentary to the 3' end of the universal promoter (i.e., primers UP-1, UP-2 and UP-3), which also contains transcription/translation regulatory elements such as the T7 promoter element, including untranslated leader sequence necessary for ribosome binding. (e.g., Figs. 1-3; p. 5, ll. 17-20). Further, the primers are used at a concentration of 50 pmol/100ul (i.e., 500 nM; claim 19), which falls in the delimited range. (e.g., p. 13, l. 7). The antisense primer would

The reference also teaches that a third DNA fragment has a 3' region that is complementary to the 5' region of a second DNA fragment. (e.g., Fig. 6, boxed portion, depicting fragment "UTL" and unlabeled fragment, with arrows depicting 5' to 3' direction). The reference teaches that the multiple DNA segments (segment 1, 2 and 3) are used in a two-step PCR process utilizing two sense and an antisense primer (primers A, B and C) to produce one amplicon comprising portions of all the segments (claims 17 and 23). Therefore, the second and third fragments can be single stranded, but even if double stranded initially, the fragments would be single stranded due to melting (claim 24).

The amplification of the overlapping segments along with the template encoding the gene of interest is at least for a portion of time (15 cycles) performed with no first or second sense primer and no antisense primer. (e.g., p. 13, Example 3, bridging to p. 14).

As such, the primer-dimer and the primer of the two sense and an antisense primer concentrations would be less than 20nM owing to the gel purification to remove said primers (claims 18 and 21). In addition, the reference teaches that the PCR-generated templates are transcribed and translated into protein products (claims 32 and 33). (e.g., pp. 14-16, Examples, 4-5; Fig. 7). In sum, Lanar et al. anticipate the rejected claims.

3. **Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Erlich et al. (US 5,314,809; see whole document).**

Erlich et al. teaches a method for amplification of a template DNA fragment, where there are two sense strands necessarily would have at least a portion of like sequence (e.g., a single nucleotide, either G, C, A or T) and an antisense primer. (e.g., Figs. 1, 2; col. 10, ll. 1-15). Therefore, the Erlich et al. anticipate the rejected claim.

4. **Claim 14 is rejected under 35 U.S.C. 102(e) as being anticipated by Sorge (US Pub. 2003/0050453; see whole document).**

Sorge teaches PCR amplification of a template DNA encoding a protein utilizing two sense primers an antisense primer (e.g., Figures 1, 6 and 10; p. 5, ¶ 0049). Therefore, Sorge anticipates the rejected claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. **Claims 14-28, 30 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanar et al. (WO 92/07949), and further in view of Rothschild et al. (US 6,303,337; hereinafter the '337 patent).**

The claims are interpreted consonant with what is stated above. In addition, the teachings of Lanar et al. are applied consonant with what is stated above. Additional claims are directed to either the second DNA fragment or the third DNA fragment comprise a sequence encoding a tag peptide, such as comprising the histidine tag peptide (i.e., 5' or 3' primer to produce a template with a C-terminal or N-terminal tag). The specification indicates that such peptides can be used in affinity separation/purification of the nascent protein.

Lanar et al. does not teach utilization of tag peptides, nor that tag peptides can consist of the native His tag peptide (i.e., SEQ ID NO: 1). However, use of affinity tags, such as His tags for purification of proteins is a well-recognized teaching in the art.

For example, the '337 patent teaches use of c-terminal and n-terminal His tag affinity markers for separation/purification of nascent proteins in a cell-free protein synthesis system. (e.g., Abstract). In addition, the '337 teaches that PCR can be used to design templates for expression in *in vitro* or *in vivo* protein expression systems, utilizing primers that contain the necessary structures/sequences for expression, such as ribosome binding sites in a prokaryotic system. (e.g., col. 9, last ¶; col. 26, last ¶ bridging to col. 27). More particularly, the reference teaches that PCR primers can be designed to incorporate affinity tags in the n- or c-terminal regions of a target protein to be expressed from a given template. (e.g., col. 27, ll. 45-65, bridging to col. 28, ¶ 1; col. 70; Example 21; col. 70, ll. 25-45; col. 72, Example 22). Furthermore, the '337 patent teaches that the His tag marker can be used. (e.g., col. 10, ¶ 1; col. 72, l. 33).

It would have been obvious to modify the PCR methods to produce a template as taught by Lanar et al. with the PCR methods taught by the '337 patent, teaching use of primers to encode affinity tagged nascent proteins, to produce a template DNA that is used in *in vitro* protein synthesis, as is contemplated by the instant disclosure. One of ordinary skill in the art would have been motivated to make such a modification to obtain the benefit of nascent protein purification/separation as the '337 patent suggests.

Given the level of skill in the art with respect to PCR, producing fusion templates and expressing proteins in an *in vitro* system, there would have been a reasonable expectation of success in incorporating the n-terminal and c-terminal primers as taught by the '337 patent into the PCR method taught by Lanar et al. to produce DNA templates encoding proteins that are amenable to cell-free expression.

6. **Claims 14-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanar et al. (WO 92/07949) and Rothschild et al. (US 6,303,337; hereinafter the '337 patent), further in view of Tchaga et al. (WO 99/57992; see whole document).**

The claims are interpreted consonant with what is stated above. Further, the teachings of Lanar et al. and the '337 patent are applied consonant with what is stated above. Additional claims are directed to the His tag as being the native His tag (i.e., SEQ ID NO: 1).

Neither Lanar et al. or the '337 patent explicitly teach that the native His tag can be utilized in utilizing primers encoding said tag in a PCR reaction to produce a DNA template.

However, Tchaga et al. teach that the metal ion binding native His tag can be used in isolating/purifying proteins. (e.g., Abstract; pp. 10-11, Example 1). More particularly, the reference teaches the sequence for the native His tag to be used in producing DNA templates that can be used to express the tagged protein and that the tag can be placed on either the c- or n-terminal side of the protein of interest. (e.g., p. 4, entire page, last ¶ bridging to p. 5).

Therefore, it would have been obvious to substitute the His tag taught by the '337 patent with the native His tag, which has been known in the art, as taught by Tchaga et al. One of ordinary skill in the art would have been motivated to utilize the native His tag so as to expand the range of potential affinity markers that could be used to produce DNA templates via PCR as is taught by the '337 patent.

Given the skill in the art at the time of invention, it would have been routine to utilize PCR methods as taught by Lanar et al. and the '337 patent to produce DNA templates with the native His tag sequence as taught by Tchaga et al., where the template could be expressed in a cell-free system and the nascent protein could be isolated/purified.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

GERRY LEFFERS
PRIMARY EXAMINER